A59

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 261/08, A61K 31/42 — A1

(11) International Publication Number: **WO 97/34881**

(43) International Publication Date: 25 September 1997 (25.09.97)

(21) International Application Number: PCT/DK97/00112

(22) International Filing Date: 14 March 1997 (14.03.97)

(30) Priority Data:
0304/96 15 March 1996 (15.03.96) DK

(71) Applicant *(for all designated States except US)*: AARHUS UNIVERSITETS FORSKNINGSFOND [DK/DK]; Aarhus Universitet, Nordre Ringgade 1, DK-8000 Aarhus C (DK).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: GOTHELF, Kurt, Vesterager [DK/DK]; Funch Thomsens Gade, 1,1 l.tv., DK-8200 Aarhus N (DK).

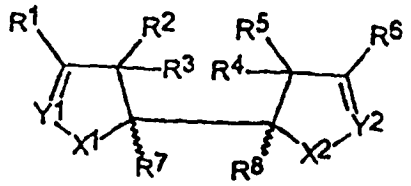
(74) Agent: PLOUGMANN, VINGTOFT & PARTNERS A/S; Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).

(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BIS-HETEROCYCLIC DERIVATIVES

(57) Abstract



(I)

Compounds of general formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each independently are: hydrogen; halogen; nitro; nitroso; cyano; a group -CO-Z-R^{10}, -CS-Z-R^{10}, -SO_2-Z-R?10?, -C(NH)-$NR^{10}R^{11}$, -CO-R^{10}, -SO-R^{10}, -SO_2-R^{10}, -Z-CO-R^{10}, -Z-CO-Z-R^{10}, -Z-CS-R^{10} or -Z-SO_2-R^{10}, -O-R^{10}, -S-R^{10} or -$NR^{10}R^{11}$, wherein each Z independently is -O-, -S- or -N(R^{11})-; optionally substituted, linear or branched C_{1-10}alkyl, C_{2-10}alkenyl, C_{4-10}alkadienyl, C_{6-10}alkatrienyl, C_{2-10}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkadienyl, C_{6-8}cycloalkatrienyl or C_{3-8}cycloalkyl-C_{1-4}alkyl; or R^3 and R^7, and/or R^4 and R^8 together form a bond; or R^1 and R^2, and/or R^5 and R^6 together form a bivalent group -$(CH_2)_n$- wherein n is an integer from 3 to 5, or a bivalent group -Z-$(C(R^{15})_2)_m$-Z- wherein m is an integer from 1 to 3; X^1 and X^2 each independently is O, S, or N(R^{12}); and Y^1 and Y^2 each independently is N or C(R^{13}); with the proviso that when X^1-Y^1 and X^2-Y^2 are both O-N, and R^3 and R^7, and R^4 and R^8, each together form a bond, then at least one of R^1, R^2, R^5, and R^6 is different from hydrogen, or that R^1 and R^6 are both different from nitro, methyl and unsubstituted phenyl; and physiologically acceptable salts thereof. Such compounds have anti-cancer properties.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Larvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

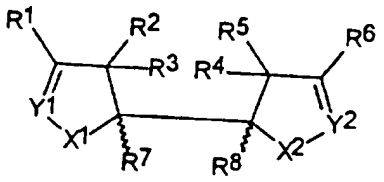
BIS-HETEROCYCLIC DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to bis-heterocyclic derivatives having anti-cancer properties.

SUMMARY OF THE INVENTION

The invention relates to compounds of the general formula I



I

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each independently are:

hydrogen;

halogen;

nitro;

nitroso;

cyano;

a group $-CO-Z-R^{10}$, $-CS-Z-R^{10}$ or $-SO_2-Z-R^{10}$ wherein Z is $-O-$, $-S-$ or $-N(R^{11})-$;

a group $-C(NH)-NR^{10}R^{11}$;

a group $-CO-R^{10}$, $-SO-R^{10}$ or $-SO_2-R^{10}$;

a group $-Z-CO-R^{10}$, $-Z-CO-Z-R^{10}$, $-Z-CS-R^{10}$ or $-Z-SO_2-R^{10}$ wherein each Z independently is as defined above;

a group $-O-R^{10}$ or $-S-R^{10}$;

a group $-NR^{10}R^{11}$;

where groups R^{10} and R^{11} each independently are hydrogen or is optionally substituted C_{1-8}alkyl, aryl, aryl-C_{1-8}alkyl where an alkyl group or moiety may be interrupted by $-O-$, $-S-$ or $-N(R^{14})-$ wherein R^{14} is hydrogen, C_{1-8}alkyl or aryl, and where the optional

substituent(s) are selected from halogen, nitro, amidine, cyano, mercapto, C_{1-8}alkylthio, arylthio, hydroxy, C_{1-8}alkoxy, aryloxy, amino, C_{1-8}alkylamino, arylamino, diC_{1-8}alkylamino, diarylamino, formyl, C_{1-8}alkylcarbonyl, arylcarbonyl, C_{1-8}alkoxycarbonyl, aryloxycarbonyl, C_{1-8}alkylcarbonyloxy, aryloxycarbonyloxy, or two neighbouring substituents together form a bivalent group $-Z-(C(R^{15})_2)_m-Z-$ wherein each Z independently is as defined above, R^{15} is hydrogen or C_{1-2}alkyl, and m is an integer from 1 to 3;

optionally substituted, linear or branched C_{1-10}alkyl, optionally substituted, linear or branched C_{2-10}alkenyl or C_{4-10}alkadienyl or C_{6-10}alkatrienyl, optionally substituted, linear or branched C_{2-10}alkynyl, or optionally substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkadienyl, C_{6-8}cycloalkatrienyl or C_{3-8}cycloalkyl-C_{1-4}alkyl where the optional substituent(s) are selected from halogen, nitro, cyano, $-CO-Z-R^{10}$, $-SO_2-Z-R^{10}$, $-CO-R^{10}$, $-SO-R^{10}$, $-SO_2-R^{10}$, $-Z-CO-R^{10}$, $-Z-SO_2-R^{10}$, $-O-R^{10}$, $-S-R^{10}$, and $-NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;

aryl or aryl-C_{1-4}-alkyl where the aryl moiety may be substituted from 1 to 6 substituents selected from C_{1-4}-alkyl, halogen, nitro, nitroso, cyano, a group $-CO-Z-R^{10}$, $-CO-Z-R^{10}$, $-SO_2-Z-R^{10}$, $-CO-R^{10}$, $-SO-R^{10}$, $-SO_2-R^{10}$, $-Z-CO-R^{10}$, $-Z-SO_2-R^{10}$, $-O-R^{10}$, $-S-R^{10}$, or $-NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;

or R^3 and R^7, and/or R^4 and R^8 together forms a bond;

or R^1 and R^2, and/or R^5 and R^6 together forms a bivalent group $-(CH_2)_n-$ wherein n is an integer from 3 to 5, or a bivalent group $-Z-(C(R^{15})_2)_m-Z-$ wherein Z, R^{15} and m is as defined above;

X^1 and X^2 each independently is O, S, or $N(R^{12})$, wherein R^{12} is a group as defined for R^{10}; and

Y^1 and Y^2 each independently is N or $C(R^{13})$ wherein R^{13} is a group as defined for R^{10} above;

with the proviso that when X^1-Y^1 and X^2-Y^2 are both O-N, and R^3 and R^7 together forms a bond, and R^4 and R^8 together forms a bond, then
at least one of R^1, R^2, R^5, and R^6 is different from hydrogen, or
R^1 and R^6 are both different from nitro, methyl and unsubstituted phenyl;
and physiologically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

In the general formula I, the wavy lines connecting R^7 and R^8 to the respective ring system indicate that each substituent in question may be in any of the two possible conformations.

In the present context, the terms "C_{1-10}alkyl" and "C_{1-8}alkyl" used to define a group or part of a group designates an alkyl group having from 1 to 10 carbon atoms and from 1 to 8 carbon atoms, respectively, and examples of such groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl. In a preferred embodiment, the alkyl group has 1-6 carbon atoms, in particular 1-4 carbon atoms. An alkoxy group designates a corresponding alkyl group bound *via* an oxygen atom.

Similarly, the term "C_{2-10}alkenyl" used to define a group or part of a group designates an alkenyl group having from 1 to 10 carbon atoms, and examples of such groups are ethenyl, 1- and 2-propenyl, 1-, 2- and 3-butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl. In a preferred embodiment, the alkenyl group has 1-6 carbon atoms, in particular 1-4 carbon atoms.

Likewise, the term "C_{4-10}alkadienyl" used to define a group or part of a group designates a diunsaturated group having from 1 to 10 carbon atoms, and examples of such groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, nonadienyl, and decadienyl.

Furthermore, the term "C_{6-10}alkatrienyl" used to define a group or part of a group designates a triunsaturated group having from 1 to 10 carbon atoms, and examples of such groups are hexatrienyl, heptatrienyl, nonatrienyl, and decatrienyl.

The term "C_{3-8}cycloalkyl" used to define a group or part of a group designates a cyclic alkyl radical of from 3 to 8 carbon atoms, and examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Likewise, the term "C_{3-8}cycloalkenyl" designates a cyclic, monounsaturated radical of from 3 to 8 carbon atoms, and examples of such groups are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. The term "C_{4-8}cycloalkadienyl" designates a cyclic, diunsaturated radical having from 4 to 8 carbon atoms, and examples of such groups are cyclopentadienyl, cyclohexadienyl, cycloheptadienyl, and cyclooctadienyl. The term "C_{6-8}cycloalkatrienyl" designates a cyclic, triunsaturated radical of from 6 to 8 carbon atoms, and examples of such groups are cycloheptatrienyl and cyclooctatrienyl.

The term "halogen" comprises fluoro, chloro, bromo and iodo.

The term "aryl" used to define a group or part of a group designates an aromatic group which may be mono-, bi- or tricyclic, and be carbocyclic or heterocyclic, as well as partially or completely hydrogenated forms of such cyclic groups. Examples of a carbocyclic aryl group are phenyl, naphthyl, indenyl, and anthracyl. A heterocyclic aryl group may be a monocyclic, 5- or 6-membered ring containing from 1 to 4, preferably 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur. Examples of such groups are pyrrolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, triazolyl, tetrazolyl, oxazinyl, thiazinyl, triazinyl, dihydropyridinyl, piperidinyl and piperidino, dihydropyranyl, tetrahydropyranyl. A heterocyclic aryl group may also be a bicyclic ring system having 8-10 members and containing from 1 or 2

heteroatoms selected from nitrogen, oxygen and sulfur. Examples of such groups are indolyl, coumaryl, purinyl, benzofuranyl, quinolinyl, isoquinolinyl, dihydroquinolinyl, dihydroisoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl.

If two neighbouring substituents together form a bivalent group $-Z-(C(R^{15})_2)_m-Z-$, a preferred example of such a bivalent substituent is $-O-(C(R^{15})_2)_m-O-$, in particular $-O-(CH_2)_m-O-$, especially $-O-CH_2-O-$ and $-O-C(CH_3)_2-O-$.

The term "physiologically acceptable salts" means salts formed with non-toxic, physiologically acceptable acids or bases of the types well known in the art of pharmaceuticals. Examples of physiologically acceptable acid addition salts are salts with inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, sulfonic, sulfanilic, nitric, phosphoric acid and the like; as well as salts with organic acids such as acetic, propionic, maleic, fumaric, benzoic, succinic, tartaric, citric, glycolic, malic, lactic, pamoic, ascorbic, stearic, phenylacetic, glutamic, salicylic acid and the like. Examples of salt with bases are salts formed with alkaline or earth alkaline metal hydroxides such as salts formed with sodium, potassium, calcium or magnesium hydroxide.

Depending on the substituents present in the general formula I, the compounds of the invention may contain one or more asymmetric carbon atoms, whereby the compound may exist in two or more isomeric forms. In such cases, the present invention as defined by the general formula I is intended to comprise each and every individual stereoisomer such as an enantiomer, as well as mixtures thereof, including racemic mixtures.

Each of the ring moieties X^1-Y^1 and X^2-Y^2 may be any of those possible in the formula. Examples of such ring moieties are $O-N$, $S-N$, $N(R^{12})-N$, $O-C(R^{13})$, $S-C(R^{13})$, and $N(R^{12})-C(R^{13})$

where R^{12} and R^{13} are as defined above. Consequently, dependent also on whether R^3 and R^7 and/or R^5 and R^8 together form a bond, each of the two rings in the formula I may independently be an isoxazole, isoxazoline, isothiazole, isothiazoline, pyrazole, pyrazoline, furan, dihydrofuran, thiophene, dihydrothiophene, pyrrol, or pyrroline ring.

In a preferred embodiment, the compounds of the invention are such in which the moieties X^1-Y^1 and X^2-Y^2 are the same, in particular where they are both O-N, i.e. that each ring independently is either an isoxazoline ring or, especially, if R^3 and R^7 together form a bond, or R^5 and R^8 together form a bond, an isoxazole ring.

It is contemplated that preferred compounds are those in which R^3 and R^7 together form a bond, and R^5 and R^8 together form a bond, i.e. each ring is an isoxazole ring, R^2 and R^5 are both hydrogen, and R^1 and R^6 independently are unsubstituted or substituted aryl groups, in particular unsubstituted phenyl or phenyl substituted with the groups defined above, in particular substituted with one to four groups selected from hydroxy, halogen, amino, alkylamino, dialkylamino, mercapto, alkylthio, nitro, sulfonyl, C_{1-8}alkoxy, C_{1-8}alkyl- or arylcarbonyloxy, C_{1-8}alkyl- or arylcarbonylamino, C_{1-8}alkyl- or arylsulfonylamino, or two neighbouring substituents together form a bivalent group -Z-$(C(R^{15})_2)_m$-Z-, wherein Z and R^{15} are as defined above.

Examples of compounds of the invention are:
5,5'-bis-(3-(4''-hydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-hydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-hydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-trihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-trihydroxyphenyl)-isoxazole),

5,5'-bis-(3-(4''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-trimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-trimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-acetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-acetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-acetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-triacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-triacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-benzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-benzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-benzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-tribenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-tribenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-hydroxy-4''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-hydroxy-3''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-methylendioxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-(2,2-propylendioxy)phenyl)-isoxazole),
5,5'-bis-(3-(4''-nitrophenyl)-isoxazole),
5,5'-bis-(3-(4''-aminophenyl)-isoxazole),
5,5'-bis-(3-(4''-acetaminophenyl)-isoxazole),
5,5'-bis-(3-(4''-chlorophenyl)-isoxazole),
5,5'-bis-(3-(4''-bromophenyl)-isoxazole),
5,5'-bis-(3-(4''-iodophenyl)-isoxazole),
5,5'-bis-(3-(4''-sulfonylphenyl)-isoxazole),

5,5'-bis-(3-(4''-amidinophenyl)-isoxazole), and
5,5'-bis-(3-(4''-carboxyphenyl)-isoxazole).

As indicated above, compounds of the invention have anti-cancer properties in that they have demonstrated growth-reducing properties in *in vitro* assays against several cancer cell lines. Examples of interesting cancer types are prostate cancer, colon cancer, CNS-cancer, non-small cell lung cancer, breast cancer, renal cancer, leukaemia, ovarian cancer, testicular cancer, lymphatic cancer, pancreatic cancer, melanoma, oesophageal cancer, stomach cancer, and intestinal cancer.

Consequently, the present invention preferably relates to those of the compounds of the general formula I which, when tested against a mammalian cancer cell line in accordance with the standard procedure of the National Cancer Institute *in vitro* Anticancer Drug Discovery Screen, results in a Percentage Growth (PG), as defined herein, below 90, preferably 80, in particular 70, especially 60, such as 50.

This screening procedure is described in detail in Boyd, M.R. & Paull, K.D.: "Some practical considerations an applications of the National Cancer Institute *in vitro* Anticancer Drug Discovery Screen", *Drug Development Research* 1995, 34, pp 91-109 and references cited therein.

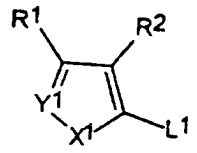
Similarly, the present invention preferably relates to those of the compounds of the general formula I which, when tested against a mammalian cancer cell line in accordance with the above indicated standard procedure exhibits a Response Parameter GI50 value, as defined herein, at a concentration of at the most 10^{-4} M with respect to at least one mammalian cancer cell line. The GI50 value may be viewed as a growth inhibitory level of effect.

Also, the present invention preferably relates to those of the compounds of the general formula I which, when tested

against a mammalian cancer cell line in accordance with the above indicated standard procedure does not exhibit a LC50 value, as defined herein, at a concentration of below 10^{-4} M. The LC50 value is the lethal concentration, "net cell killing" or cytotoxicity parameter.

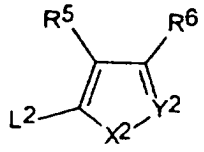
The compounds of the invention may be prepared by methods known *per se* in the art. Thus, the compounds in which and R^3 and R^7 together form a bond, and R^4 and R^8 together form a bond may be prepared by any known reaction for the cross-coupling between two aromatic five-membered rings. Examples of such reactions are the Stille cross-coupling reaction (Stille, J.K., *Angew. Chem.* 1986, *1986*, p 504) and the Suzuki reaction (Miyaura, N.; Ishiyama. T.; Sasaki, H.; Ihikawa, M.; Suzuki, A., *J.Am.Chem.Soc.* 1989, *111*, p 314).

Thus, a compound of the general formula II



II

in which R^1, R^2, X^1, and Y^1 are as defined above, and L^1 is Cl, Br, I or $-O-SO_2-CF_3$, is reacted with a compound of the general formula III



III

in which R^5, R^6, X^2, and Y^2 are as defined above, and L^2 is $-SnBu_3$ (where Bu designates n-butyl) or $-B(OH)_2$ in the presence of a catalytic amount of a palladium catalyst such as $Pd(PPh_3)_4$ or $Pd(AsPh_3)_4$ (where Ph designates phenyl). The reaction is usually carried out under an inert gas in an organic aprotic, polar solvent such as dioxan or tetrahydrofuran, at a temperature between room temperature and the boiling point of the solvent, for a period of from 1 to 48 hours.

When the two ring systems and their substituents in the compound to be prepared are identical, the synthesis may also be carried out by reacting a compound of the formula II alone or a compound of the formula III alone under the above conditions with the exception that a Pd(II) compound such as $PdCl_2$ or $PdCl_2(PPh_3)_2$ is used, preferably in an amount of at least 0.5 mole equivalent calculated on the compound II or III.

Furthermore, compounds in which X^1-Y^1 and X^2-Y^2 are both O-N, and R^2, R^3, R^4 and R^5 are all hydrogen, may be prepared by reacting a compound of the general formula IV

$$R^1\text{-}CH{=}N\text{-}OH \qquad \text{IV}$$

with a halogenating agent, preferably a chlorinating agent such as N-chlorosuccinimide, followed by treatment with a base to give the corresponding nitrile oxide, followed immediately by treatment with one mole equivalent of a compound of the formula V

$$H_2C{=}C(R^7)\text{-}C(R^8){=}CH_2 \qquad \text{V}$$

After a period of time in the order of 0.5 to 2 hours, the resulting 5-vinyl-isoxazoline intermediate is treated with a nitrile oxide generated from a compound of the general formula VI

$$R^6\text{-}CH{=}N\text{-}OH \qquad \text{VI}$$

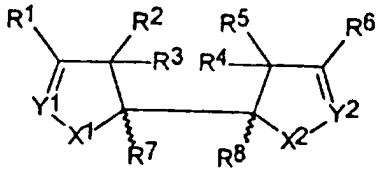
in the same manner as described above for formula IV.

The nitrile oxide preparation step(s) may be carried out in a aprotic polar solvent such as chloroform, dichloromethane or ethyl acetate, at temperatures between 0 and 80°C. After stirring for a period, the subsequent 1,3-elimination of HCl to give the nitrile oxide is normally carried out at temperatures from -20 to +50°C with a mild base such as $KHCO_3$, dilute triethylamine, dilute pyridine or the like.

The compounds wherein X^1-Y^1 and X^2-Y^2 are both O-N, and R^3 and R^7 together form a bond, and R^4 and R^8 together form a bond, may also be prepared in a method similar to the one described above involving the compounds IV, V, and VI. The difference lies in the fact that following the reaction with the nitrile oxide generated from the compound VI, an elimination reaction is carried out, and this is made possible by using a compound of the general formula V in which R^7 and R^8 are both groups capable of undergoing a 1,2-elimination reaction with a hydrogen atom on the neighbouring carbon atom. Examples of such groups are Br, Cl, I, trialkylsilyloxy such as trimethylsilyloxy, or morpholino, and the elimination is carried out by treatment with acid or base, dependent on which type of group is used as R^7 and R^8, as it will be familiar to the person skilled in the art.

The starting compounds of the formulas II, III, IV, V, and VI are known compounds or may be prepared according to procedures known in the art (see i.a. (a) Kondo, Y.; Uchiyama, D.; Sakamoto, T.; Yamanaka, H. *Tetrahedron Lett.* 1989, *30*, p 4249, and (b) Hansson, L.; Carlson, R. *Acta Chem. Scand.* 1989, *43*, p 304).

The invention further relates to a pharmaceutical composition comprising one or more of the compounds of the general formula I'



I'

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each independently are:

hydrogen;

halogen;

nitro;

nitroso;

cyano;

a group $-CO-Z-R^{10}$, $-CS-Z-R^{10}$ or $-SO_2-Z-R^{10}$ wherein Z is $-O-$, $-S-$ or $-N(R^{11})-$;

a group $-C(NH)-NR^{10}R^{11}$;

a group $-CO-R^{10}$, $-SO-R^{10}$ or $-SO_2-R^{10}$;

a group $-Z-CO-R^{10}$, $-Z-CO-Z-R^{10}$, $-Z-CS-R^{10}$ or $-Z-SO_2-R^{10}$ wherein each Z independently is as defined above;

a group $-O-R^{10}$ or $-S-R^{10}$;

a group $-NR^{10}R^{11}$;

where groups R^{10} and R^{11} each independently are hydrogen or is optionally substituted C_{1-8}alkyl, aryl, aryl-C_{1-8}alkyl where an alkyl group or moiety may be interrupted by $-O-$, $-S-$ or $-N(R^{14})-$ wherein R^{14} is hydrogen, C_{1-8}alkyl or aryl, and where the optional substituent(s) are selected from halogen, nitro, amidine, cyano, mercapto, C_{1-8}alkylthio, arylthio, hydroxy, C_{1-8}alkoxy, aryloxy, amino, C_{1-8}alkylamino, arylamino, diC_{1-8}alkylamino, diarylamino, formyl, C_{1-8}alkylcarbonyl, arylcarbonyl, C_{1-8}alkoxycarbonyl, aryloxycarbonyl, C_{1-8}alkylcarbonyloxy, aryloxycarbonyloxy, or two neighbouring substituents together form a bivalent group $-Z-(C(R^{15})_2)_m-Z-$ wherein each Z

independently is as defined above, R^{15} is hydrogen or C_{1-2}alkyl, and m is an integer from 1 to 3;
optionally substituted, linear or branched C_{1-10}alkyl, optionally substituted, linear or branched C_{2-10}alkenyl or C_{4-10}alkadienyl or C_{6-10}alkatrienyl, optionally substituted, linear or branched C_{2-10}alkynyl, or optionally substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkadienyl, C_{6-8}cycloalkatrienyl or C_{3-8}cycloalkyl-C_{1-4}alkyl where the optional substituent(s) are selected from halogen, nitro, cyano, -CO-Z-R^{10}, -SO_2-Z-R^{10}, -CO-R^{10}, -SO-R^{10}, -SO_2-R^{10}, -Z-CO-R^{10}, -Z-SO_2-R^{10}, -O-R^{10}, -S-R^{10}, and -$NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above; aryl or aryl-C_{1-4}-alkyl where the aryl moiety may be substituted from 1 to 6 substituents selected from C_{1-4}-alkyl, halogen, nitro, nitroso, cyano, a group -CO-Z-R^{10}, -CO-Z-R^{10}, -SO_2-Z-R^{10}, -CO-R^{10}, -SO-R^{10}, -SO_2-R^{10}, -Z-CO-R^{10}, -Z-SO_2-R^{10}, -O-R^{10}, -S-R^{10}, or -$NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;
or R^3 and R^7, and/or R^4 and R^8 together forms a bond;
or R^1 and R^2, and/or R^5 and R^6 together forms a bivalent group -$(CH_2)_n$- wherein n is an integer from 3 to 5, or a bivalent group -Z-$(C(R^{15})_2)_m$-Z- wherein Z, R^{15} and m is as defined above;

X^1 and X^2 each independently is O, S, or N(R^{12}), wherein R^{12} is a group as defined for R^{10} above; and

Y^1 and Y^2 each independently is N or C(R^{13}) wherein R^{13} is a group as defined for R^{10} above;
in combination with a pharmaceutically acceptable carrier.

The compounds of the invention are conveniently administered to warm-blooded animals, e.g. mammals such as humans, orally, parenterally (e.g. intravenously, intramuscularly or intraperitoneally), topically, or rectally in dosage forms containing conventional, non-toxic, pharmaceutically acceptable carriers, adjuvants and vehicles. The formulation and preparation of any of this spectrum of dosage forms into which

the compounds of the invention can be disposed is well-known to those skilled in the art of pharmaceutical formulation. Specific information and techniques may, however, be found in the text entitled "Remington's Pharmaceutical Sciences" Sixteenth Edition, 1980.

The pharmaceutical compositions containing the compounds of the invention may be in a form suitable for oral use, e.g. as tablets, troches, lozenges, aqueous or oily suspensions, solutions, or emulsions, dispersible powders or granules, hard or soft capsules, syrups or elixirs. The compositions for oral use include tablets which contain the active ingredient in admixture with non-toxic, pharmaceutically acceptable excipients such as inert diluents, e.g. calcium carbonate, sodium chloride, lactose, calcium phosphate, or sodium phosphate; granulating and disintegrating agents, e.g. potato starch or alginic acid; binding agents, e.g. starch, gelatin or acacia; and lubricating agents, e.g. magnesium stearate, stearic acid or talc. The tablets may be uncoated or be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract to provide sustained action.

Oral formulations may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium such as peanut or olive oil or liquid paraffin.

Aqueous suspension usually contain the active compounds in admixture with suitable excipients such as suspending agents, e.g. sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide e.g. lecithin, a condensation product of ethylene oxide with a long-chain alcohol (e.g. heptadecaethyleneoxycetanol), with a partial

ester derived from fatty acids and a hexitol (e.g. polyethylene sorbitol monooleate), and with a partial ester derived from fatty acids and hexitol anhydrides (e.g. polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives such as methyl, ethyl or n-propyl p-methoxybenzoate, as well as colouring, sweetening or flavouring agents.

A composition for parenteral administration may be a sterile solution or an aqueous or oleaginous emulsion or suspension. Such compositions may be formulated according to the known art using suitable well-known dispersing or wetting agents selected among those mentioned above. The sterile injectable preparation may be a sterile injectable solution or suspension in a parenterally acceptable diluent or solvent such as sterile, pyrogen-free water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution.

The compounds of formula I may also be administered in the form of suppositories for rectal administration of the compounds. Such compositions may be prepared by mixing the compound with a suitable non-irritating excipient which is solid at normal temperature but liquid at the rectal temperature, e.g. cocoa butter or *adeps solidus* polyethylene glycols.

In therapeutic applications, the compounds of the invention or the pharmaceutical compositions containing them are administered to a patient in an amount sufficient to produce the desired effect, defined as a "therapeutically effective dose". The therapeutically effective dose of a compound of the invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration, the health and condition of the patient, and the judgement of the prescribing physician. For example, the dose for continuous infusion will typically be in the range of about 10 μg to about 5 g per day for a 70 kg patient, preferably between about 0.1 mg and about 1 g.

The invention is further illustrated by the following, non-limiting examples.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Gemini spectrometer at 200 MHz or 300 MHz. Chemical shifts for ^1H NMR are reported in ppm downfield from tetramethylsilane (TMS). Mass spectra were recorded on a Varian Gemini Micro-Mass 7070F spectrometer operating at 70 eV with a direct inlet. Preparative thin layer chromatography (PTLC) was performed on 200x200x1,8 mm silica gel ($PF_{254+366}$, Merck) on glass plates. Solvents were dried using standard procedures.

EXAMPLE 1

Bis 5,5'-(3-(4''-hydroxyphenyl)isoxazole) (1a), Method A:
In a 100 mL round bottom flask containing a 30 mm teflon-coated magnetic stirring bar and 50 mL of EtOAc, 4-hydroxybenzaldehyde oxime (2,057 g, 15 mmol) was placed. After stirring for 5 min at room temperature, N-chlorosuccinimide (2,128 g, 16 mmol) was added. The mixture was stirred at room temperature for 2 h. Thereafter, bis-2,3-(trimethylsilyloxy)-1,3-butadiene (1,151 g, 5 mmol) was added. After 1 min., a solution of triethylamine (1,162 g,16 mmol) in EtOAc (10 mL) was added over a period of 5 min. The reaction mixture was stirred for 3 h at room temperature. The mixture was filtered through a layer of celite and the solvent of the filtrate was evaporated in vacuo. The precipitate was dissolved in 10 mL of glacial acetic acid and conc. H_2SO_4 (0,5 mL) was added to the mixture. A reflux condenser was fitted to the flask and the flask was placed in an oil bath at 120°C with stirring for 2h. Water (20 mL) was added and the mixture was cooled to room temperature. The precipitate was filtered off, and washed with H_2O (10 mL). After drying, the residue was purified by column chromatography (Et_2O:petroleum ether,

2:1). The product was recrystallized from acetonitrile to give compound **1a**.

^{1}H NMR (Acetone d_6) δ: 6,90 (d, J=8,9 Hz, 4H), 7,05 (s, 2H), 7,68 (d, J=8,9 Hz, 4H);

MS *mz*=320 (M^+).

EXAMPLE 2

Bis-5,5'-(3-(4''-hydroxyphenyl)isoxazole) (1a): Method B:

In a 5 mL round bottom flask, a 10 mm teflon coated stirring bar, dry dioxane (2 mL) and 3-(4'-hydroxyphenyl)-5-(tributyl-stannyl)-isoxazole (450 mg, 1 mmol) was placed under nitrogen. $PdCl_2$ (88,7 mg, 0,5 mmol) was added to the solution. The flask was fitted with a reflux condenser and heated on a oil bath at 100°C. The mixture was stirred at this temperature for 24 h. The crude mixture was cooled to room temperature and filtered through a layer of celite (10 mm). The solvent was removed by evaporation *in vacuo*. The residue was purified by preparative thin layer chromatography (PTLC) (Et_2O:petroleum ether; 2:1, rf=0,4). The solid product was recrystallized from acetonitrile to give **1a** (30 mg, 6%) as white crystals.

^{1}H NMR (Acetone d_6) δ: 6,90 (d, J=8,9 Hz, 4H), 7,05 (s, 2H), 7,68 (d, J=8,9 Hz, 4H);

MS *mz*=320 (M^+).

EXAMPLE 3

Bis-5,5'-(3-(4-hydroxyphenyl)-isoxazoline)(2a):

In a 100 mL round bottom flask containing a 30 mm teflon-coated magnetic stirring bar and 50 mL of ethyl acetate, 4-hydroxybenzaldehyde oxime (2,057 g, 15 mmol) was placed. After stirring for 5 min at room temperature, N-chlorosuccinimide (2,128 g, 16 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction flask was cooled to -15°C in a ice/NaCl bath, and the flask was sealed with a rubber septum. Liquid 1,3-butadiene (400 µL g, 5 mmol) cooled to -78°C was added through the septum via a syringe.

After 1 min, a solution of triethylamine (1,162 g, 16 mmol) in EtOAc 10 mL was added over a period of 5 min. The reaction mixture was heated to room temperature and stirred for 3 h. The solvent was removed by evaporation *in vacuo* and the residue was dissolved in 5 mL of a mixture of 5% MeOH in CH_2Cl_2. The crude product was purified by column chromatography on silica gel (200 g, 5% MeOH in CH_2Cl_2). The selected fractions containing minor byproduct impurities was recrystallized in MeOH/CH_2Cl_2 to give pure **2a** as a single diastereomer (430 mg, 32%). mp=265-270°C (dec.)
^1H NMR (Acetone d_6) δ: 3,27 (dd, J= 17,33, 6,67 Hz, 2H), 3,53 (dd, J=17,33, 9,33 Hz, 2H), 4,79 (m, 2H), 6,90 (d, J=9,07 Hz, 4H), 7,68 (d, J=9,07 Hz, 4H);
MS *mz*=324 (M^+).

TEST EXAMPLE

The NCI *in vitro* disease-oriented primary antitumour screen used for testing compounds of the invention has been published in *Seminars in Oncology*, 1992, *19*, page 622-638. The test compound, bis-5,5'-(3-(4''-hydroxyphenyl)-isoxazole), was tested on a total of 60 cell lines representing 9 different types of cancer, the tests being conducted at a minimum of five concentrations at 10-fold dilutions. A 48 hours continuous drug exposure protocol was used, and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth.

The Calculated Measurement of Effect: Percentage Growth (PG)

The measured effect of the compound on a cell line was calculated according to one or the other of the following two expressions:

If (Mean OD_{test} - Mean OD_{tzero}) $\geq$ 0, then
PG = 100 x (Mean OD_{test} - Mean OD_{tzero}) / (Mean OD_{ctrl} - Mean OD_{tzero})

If (Mean OD_{test} - Mean OD_{tzero}) < 0, then

$$PG = 100 \times (\text{Mean } OD_{test} - \text{Mean } OD_{tzero}) / \text{Mean } OD_{tzero}$$

where:

Mean OD_{tzero} = The average of optical density measurements of SRB-derived colour just before exposure of cells to the test compound.

Mean OD_{test} = The average of optical density measurements of SRB-derived colour after 48 hours of exposure of cells to the test compound.

Mean OD_{ctrl} = The average of optical density measurements of SRB-derived colour after 48 hours with no exposure of cells to the test compound.

The data obtained are shown in Table 1 and 2 below.

TABLE 1

Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities -8.0	-7.0	-6.0	-5.0	Log10 Concentration -4.0	-8.0	Percent Growth -7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.706	1.898	1.856	1.836	1.283	0.876	0.743	96	95	48	14	3	9.24E-07	>1.00E-04	>1.00E-04
HL-60(TB)	0.481	2.379	2.199	2.119	1.537	0.880	0.585	91	86	56	21	5	1.45E-06	>1.00E-04	>1.00E-04
K-562	0.403	1.389	1.334	1.334	1.054	0.756	0.492	94	94	66	36	9	3.40E-06	>1.00E-04	>1.00E-04
MOLT-4	0.814	2.074	2.067	1.958	1.600	0.892	0.716	99	91	62	6	-12	1.66E-06	2.70E-05	>1.00E-04
RPMI-8226	0.803	2.272	2.383	2.224	1.827	1.297	1.164	108	97	70	34	25	3.52E-06	>1.00E-04	>1.00E-04
SR	0.504	2.224	2.166	2.174	1.746	1.111	0.977	97	97	72	35	.	3.99E-06	.	.
Non-Small Cell Lung Cancer															
A549/ATCC	0.235	1.290	1.322	1.283	1.230	0.914	0.734	103	99	94	64	47	6.98E-05	>1.00E-04	>1.00E-04
EKVX	0.883	1.907	1.902	1.896	1.836	1.549	1.235	99	99	93	65	34	3.09E-05	>1.00E-04	>1.00E-04
HOP-62	0.324	1.200	1.179	1.145	1.117	0.923	0.534	98	94	90	68	24	2.59E-05	>1.00E-04	>1.00E-04
HOP-92	0.450	1.025	0.978	1.043	1.015	0.984	0.891	92	103	98	93	77	>1.00E-04	>1.00E-04	>1.00E-04
NCI-H226	1.047	1.939	1.967	1.931	1.940	1.940	1.762	103	99	100	100	80	>1.00E-04	>1.00E-04	>1.00E-04
NCI-H23	0.467	0.821	0.803	0.850	0.821	0.813	0.729	95	108	100	98	74	>1.00E-04	>1.00E-04	>1.00E-04
NCI-H322M	0.579	1.988	1.976	1.973	1.956	1.615	1.390	99	99	98	74	58	>1.00E-04	>1.00E-04	>1.00E-04
NCI-H460	0.055	0.563	0.597	0.595	0.629	0.549	0.270	107	106	113	97	42	7.24E-05	>1.00E-04	>1.00E-04
NCI-H522	0.295	0.938	0.915	0.925	0.876	0.751	0.343	97	98	90	71	7	2.14E-05	>1.00E-04	>1.00E-04
Colon Cancer															
COLO 205	0.423	1.489	1.581	1.523	1.590	1.548	1.355	109	103	110	106	87	>1.00E-04	>1.00E-04	>1.00E-04
HCC-2998	0.492	0.905	0.868	0.932	0.868	0.860	0.592	91	106	91	89	24	4.03E-05	>1.00E-04	>1.00E-04
HCT-116	0.371	1.859	1.822	1.794	1.651	1.227	1.039	98	96	86	58	45	3.94E-05	>1.00E-04	>1.00E-04
HCT-15	0.472	1.878	1.837	1.639	1.079	0.822	0.810	97	83	43	25	24	6.74E-07	>1.00E-04	>1.00E-04
HT29	0.148	1.301	1.079	1.215	1.208	1.076	0.803	81	93	92	81	57	>1.00E-04	>1.00E-04	>1.00E-04
KM12	0.315	1.305	1.339	1.344	1.180	0.815	0.715	103	104	87	51	40	1.13E-05	>1.00E-04	>1.00E-04
SW-620	0.232	1.262	1.209	1.220	1.073	0.860	0.884	95	96	82	61	63	>1.00E-04	>1.00E-04	>1.00E-04
CNS Cancer															
SF-268	0.614	1.054	1.001	0.935	0.963	0.925	0.697	88	73	79	71	19	2.51E-05	>1.00E-04	>1.00E-04
SF-295	0.386	1.141	1.139	1.154	1.057	0.874	0.754	100	102	89	65	49	8.35E-05	>1.00E-04	>1.00E-04
SF-539	1.060	2.069	2.028	2.030	1.954	1.214	0.809	96	96	89	15	-24	3.36E-06	2.47E-05	>1.00E-04
SNB-19	0.266	0.716	0.695	0.692	0.749	0.730	0.533	95	95	107	103	59	>1.00E-04	>1.00E-04	>1.00E-04
SNB-75	0.338	0.848	0.772	0.771	0.739	0.754	0.393	85	85	79	82	11	2.79E-05	>1.00E-04	>1.00E-04
U251	0.074	0.521	0.370	0.432	0.420	0.346	0.261	66	80	77	61	42	3.71E-05	>1.00E-04	>1.00E-04

TABLE 1 continued

Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities (Log10 Concentration) -8.0	-7.0	-6.0	-5.0	-4.0	-8.0	Percent Growth -7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Melanoma															
LOX IMVI	0.158	0.794	0.799	0.826	0.793	0.735	0.435	101	105	100	91	44	7.29E-05	>1.00E-04	>1.00E-04
MALME-3M	0.624	1.651	1.622	1.528	1.623	1.307	1.064	97	88	97	67	43	4.97E-05	>1.00E-04	>1.00E-04
M14	0.108	0.769	0.732	0.817	0.581	0.460	0.498	94	107	72	53	59	>1.00E-04	>1.00E-04	>1.00E-04
SK-MEL-2	0.598	1.035	1.013	1.004	0.984	0.871	0.721	95	93	88	62	28	2.30E-05	>1.00E-04	>1.00E-04
SK-MEL-28	0.206	0.721	0.730	0.742	0.726	0.668	0.579	102	104	101	90	72	>1.00E-04	>1.00E-04	>1.00E-04
SK-MEL-5	0.377	1.909	1.933	1.854	1.873	1.230	0.869	102	96	98	56	32	1.74E-05	>1.00E-04	>1.00E-04
UACC-257	0.626	1.761	1.725	1.740	1.661	1.243	0.992	97	98	91	54	32	1.57E-05	>1.00E-04	>1.00E-04
Ovarian Cancer															
IGROV1	0.501	1.825	1.732	1.732	1.480	1.253	1.143	93	93	74	57	49	6.65E-05	>1.00E-04	>1.00E-04
OVCAR-4	0.083	0.736	0.725	0.744	0.666	0.514	0.477	98	101	89	66	60	>1.00E-04	>1.00E-04	>1.00E-04
OVCAR-5	0.483	0.888	0.827	0.795	0.838	0.784	0.820	85	77	88	74	83	>1.00E-04	>1.00E-04	>1.00E-04
OVCAR-8	0.286	1.374	1.431	1.450	1.377	1.124	0.890	105	107	100	77	55	>1.00E-04	>1.00E-04	>1.00E-04
Renal Cancer															
786-0	0.205	0.957	0.910	1.066	1.024	0.882	0.700	94	114	109	90	66	>1.00E-04	>1.00E-04	>1.00E-04
ACHN	0.422	1.780	1.760	1.746	1.275	0.941	0.847	99	97	63	38	31	3.31E-06	>1.00E-04	>1.00E-04
CAKI-1	0.379	1.197	1.128	1.125	0.996	1.005	0.741	91	91	75	77	44	6.61E-05	>1.00E-04	>1.00E-04
SN12C	0.499	2.550	2.349	2.547	1.375	1.054	0.938	90	100	43	27	21	7.46E-07	>1.00E-04	>1.00E-04
TK-10	0.609	1.495	1.503	1.505	1.466	1.250	1.146	101	101	97	72	61	>1.00E-04	>1.00E-04	>1.00E-04
Prostate Cancer															
PC-3	0.234	1.065	0.934	1.011	0.998	0.766	0.617	84	93	92	64	46	6.06E-05	>1.00E-04	>1.00E-04
DU-145	0.554	1.228	1.182	1.238	1.095	0.854	0.812	93	101	80	45	38	7.05E-06	>1.00E-04	>1.00E-04
Breast Cancer															
MCF7	0.125	0.619	0.486	0.423	0.514	0.435	0.167	73	60	79	63	8	1.72E-05	>1.00E-04	>1.00E-04
MCF7/ADR-RES	0.305	1.136	1.123	1.141	1.110	0.920	0.852	98	101	97	74	66	>1.00E-04	>1.00E-04	>1.00E-04
MDA-MB-231/ATCC	0.448	2.218	2.285	2.037	1.776	1.204	1.100	104	90	75	43	37	5.95E-06	>1.00E-04	>1.00E-04
MDA-MB-435	0.163	0.875	0.453	0.719	0.597	0.322	0.253	41	78	61	22	13		>1.00E-04	>1.00E-04
BT-549	0.641	1.424	1.420	1.391	1.467	1.323	1.010	100	96	106	87	47	8.45E-05	>1.00E-04	>1.00E-04

TABLE 2

Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities Log10 Concentration -8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.271	0.802	0.816	0.766	0.516	0.348	0.414	103	93	46	15	27	8.24E-07	>1.00E-04	>1.00E-04
HL-60(TB)	0.223	0.677	0.736	0.716	0.549	0.437	0.345	113	109	72	47	27	7.75E-06	>1.00E-04	>1.00E-04
K-562	0.338	0.657	0.624	0.702	0.488	0.362	0.367	90	114	47	8	9	9.00E-07	>1.00E-04	>1.00E-04
MOLT-4	0.622	0.770	0.805	0.826	0.701	0.414	0.375	124	138	53	-33	-40	1.10E-06	4.12E-06	>1.00E-04
SR	0.355	0.840	0.805	0.820	0.744	0.714	0.593	93	96	80	74	49	9.12E-05	>1.00E-04	>1.00E-04
Non-Small Cell Lung Cancer															
A549/ATCC	0.242	1.304	1.296	1.269	1.186	0.896	0.674	99	97	89	62	41	3.58E-05	>1.00E-04	>1.00E-04
EKVX	0.529	1.316	1.254	1.280	1.127	1.029	0.730	92	95	76	63	26	2.27E-05	>1.00E-04	>1.00E-04
HOP-62	0.333	0.859	0.692	0.711	0.701	0.653	0.621	68	72	70	61	55	>1.00E-04	>1.00E-04	>1.00E-04
HOP-92	0.462	0.827	0.824	0.813	0.825	0.800	0.656	99	96	99	93	53	>1.00E-04	>1.00E-04	>1.00E-04
NCI-H226	0.810	1.591	1.539	1.536	1.439	1.394	1.140	93	93	80	75	42	5.76E-05	>1.00E-04	>1.00E-04
NCI-H23	0.369	1.335	1.401	1.328	1.359	1.256	1.076	107	99	102	92	73	>1.00E-04	>1.00E-04	>1.00E-04
NCI-H322M	0.613	1.742	1.676	1.661	1.645	1.431	1.161	94	93	91	72	49	8.71E-05	>1.00E-04	>1.00E-04
NCI-H460	0.094	0.607	0.600	0.595	0.554	0.411	0.252	98	98	90	62	31	2.39E-05	>1.00E-04	>1.00E-04
NCI-H522	0.381	1.108	1.079	1.071	0.938	0.831	0.498	96	95	77	62	16	1.81E-05	>1.00E-04	>1.00E-04
Colon Cancer															
COLO 205	0.316	1.299	1.237	1.381	1.384	1.460	1.003	94	108	109	116	70	>1.00E-04	>1.00E-04	>1.00E-04
HCC-2998	0.278	0.577	0.489	0.490	0.507	0.594	0.479	70	71	77	105	67	>1.00E-04	>1.00E-04	>1.00E-04
HCT-116	0.259	1.964	1.806	1.836	1.736	1.262	1.052	91	92	87	59	47	5.20E-05	>1.00E-04	>1.00E-04
HCT-15	0.136	0.827	0.769	0.740	0.613	0.441	0.452	92	87	69	44	46	5.80E-06	>1.00E-04	>1.00E-04
HT29	0.242	1.647	1.650	1.674	1.645	1.755	1.394	100	102	100	108	82	>1.00E-04	>1.00E-04	>1.00E-04
KM12	0.246	1.178	1.227	1.217	0.999	0.725	0.581	105	104	81	51	36	1.24E-05	>1.00E-04	>1.00E-04
SW-620	0.283	1.624	1.666	1.505	1.219	0.944	0.768	103	91	70	49	36	9.22E-06	>1.00E-04	>1.00E-04
CNS Cancer															
SF-268	0.397	1.177	1.132	1.118	1.084	0.939	0.756	94	92	88	69	46	6.76E-05	>1.00E-04	>1.00E-04
SF-295	0.335	1.132	1.089	1.105	1.007	0.756	0.624	94	97	84	53	36	1.47E-05	>1.00E-04	>1.00E-04
SF-539	0.496	1.348	1.321	1.293	1.185	0.813	0.543	97	94	81	37	6	5.09E-06	>1.00E-04	>1.00E-04
SNB-75	0.398	0.801	0.820	0.765	0.755	0.777	0.681	105	91	89	94	70	>1.00E-04	>1.00E-04	>1.00E-04
U251	0.180	1.189	1.151	1.133	1.103	1.004	0.499	96	94	91	82	32	4.29E-05	>1.00E-04	>1.00E-04
Melanoma															
LOX IMVI	0.311	1.578	1.618	1.410	0.997	0.794	0.628	103	87	54	38	25	1.81E-06	>1.00E-04	>1.00E-04
MALME-3M	0.551	1.512	1.491	1.486	1.403	1.252	0.904	98	97	89	73	37	4.29E-05	>1.00E-04	>1.00E-04
M14	0.318	1.075	0.880	0.915	0.859	0.698	0.626	74	79	71	50	41	1.05E-05	>1.00E-04	>1.00E-04
SK-MEL-2	0.683	1.386	1.274	1.309	1.223	1.108	1.069	84	89	77	60	55	>1.00E-04	>1.00E-04	>1.00E-04
SK-MEL-28	0.220	0.781	0.782	0.719	0.742	0.698	0.511	100	89	93	85	52	>1.00E-04	>1.00E-04	>1.00E-04
SK-MEL-5	0.361	1.645	1.606	1.635	1.592	1.488	0.944	97	99	96	88	45	7.80E-05	>1.00E-04	>1.00E-04
UACC-257	0.868	1.217	1.474	1.469	1.281	0.854	0.857	174	172	119	-2	-1	3.72E-06	9.69E-06	>1.00E-04
UACC-62	0.362	1.429	1.481	1.410	0.917	0.580	0.586	105	98	52	20	21	1.16E-06	>1.00E-04	>1.00E-04

TABLE 2 continued

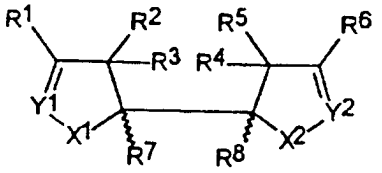
Panel/Cell Line	Time Zero	Ctrl	Mean Optical Densities Log10 Concentration -8.0	-7.0	-6.0	-5.0	-4.0	-8.0	Percent Growth -7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Ovarian Cancer															
IGROV1	0.549	1.715	1.684	1.668	1.509	1.261	0.979	97	96	82	61	37	2.86E-05	>1.00E-04	>1.00E-04
OVCAR-3	0.447	1.133	1.048	1.015	0.970	0.918	0.912	88	83	76	69	68	>1.00E-04	>1.00E-04	>1.00E-04
OVCAR-4	0.153	0.653	0.621	0.595	0.582	0.458	0.459	94	88	86	61	61	>1.00E-04	>1.00E-04	>1.00E-04
OVCAR-5	0.514	1.360	1.144	1.178	1.058	1.038	0.816	74	78	64	62	36	2.85E-05	>1.00E-04	>1.00E-04
OVCAR-8	0.425	1.398	1.314	1.389	1.254	1.061	0.997	91	99	85	65	59	>1.00E-04	>1.00E-04	>1.00E-04
SK-OV-3	0.370	0.856	0.824	0.766	0.744	0.736	0.627	93	81	77	75	53	>1.00E-04	>1.00E-04	>1.00E-04
Renal Cancer															
786-0	0.251	1.329	1.312	1.298	1.193	1.074	0.801	98	97	87	76	51	>1.00E-04	>1.00E-04	>1.00E-04
A498	0.447	1.172	1.141	1.118	1.133	1.088	1.032	96	93	95	88	81	>1.00E-04	>1.00E-04	>1.00E-04
ACHN	0.121	0.996	1.020	0.881	0.591	0.505	0.538	103	87	54	44	48	2.39E-06	>1.00E-04	>1.00E-04
CAKI-1	0.637	1.575	1.527	1.686	1.581	1.349	0.995	95	112	101	76	38	4.86E-05	>1.00E-04	>1.00E-04
RXF 393	0.334	0.790	0.761	0.750	0.736	0.764	0.610	93	91	88	94	61	>1.00E-04	>1.00E-04	>1.00E-04
SN12C	0.364	1.021	0.988	0.958	0.920	0.927	0.793	95	90	85	86	65	>1.00E-04	>1.00E-04	>1.00E-04
TK-10	0.813	1.769	1.753	1.706	1.618	1.483	1.387	98	93	84	70	60	>1.00E-04	>1.00E-04	>1.00E-04
UO-31	0.534	1.435	1.433	1.424	1.263	0.990	0.836	100	99	81	51	34	1.08E-05	>1.00E-04	>1.00E-04
Prostate Cancer															
PC-3	0.528	1.738	1.594	1.579	1.328	0.905	0.697	88	87	66	31	14	2.89E-06	>1.00E-04	>1.00E-04
DU-145	1.014	2.673	2.564	2.531	2.139	1.617	1.362	93	91	68	36	21	3.68E-06	>1.00E-04	>1.00E-04
Breast Cancer															
MCF7	0.183	0.982	1.010	0.958	0.962	0.830	0.533	104	97	98	81	44	6.82E-05	>1.00E-04	>1.00E-04
MCF7/ADR-RES	0.474	1.606	1.615	1.547	1.544	1.294	1.099	101	95	94	72	55	>1.00E-04	>1.00E-04	>1.00E-04
MDA-MB-231/ATCC	0.446	1.063	1.080	1.059	1.045	1.031	0.832	103	99	97	95	63	>1.00E-04	>1.00E-04	>1.00E-04
HS 578T	0.568	1.060	0.977	0.946	1.036	0.981	0.851	83	77	95	84	57	>1.00E-04	>1.00E-04	>1.00E-04
MDA-MB-435	0.268	1.233	1.310	1.218	1.144	0.871	0.759	108	98	91	63	51	>1.00E-04	>1.00E-04	>1.00E-04
MDA-N	0.428	1.713	1.618	1.604	1.476	1.182	0.986	93	91	82	59	43	3.69E-05	>1.00E-04	>1.00E-04
BT-549	0.515	1.593	1.762	1.150	1.108	1.014	1.035	.	59	55	46	48	3.77E-06	>1.00E-04	>1.00E-04
T-47D	0.453	1.057	1.052	1.057	0.926	0.792	0.721	99	100	78	56	44	3.31E-05	>1.00E-04	>1.00E-04

The tables present the experimental data collected against each cell line. The first two columns describe the subpanel (e.g. leukaemia) and cell line (e.g. CCRF-CEM) involved. The next two columns list the Mean OD_{tzero} and Mean OD_{ctrl}; the next five columns list the Mean OD_{test} for each of five different concentrations. Each concentration is expressed as the $\log_{10}$ (molar or μg/ml). The next five columns list the calculated PGs for each concentration. The response parameters GI50, TGI, and LC50 are interpolated values representing the concentrations at which the PG is +50, 0, and -50, respectively. Sometimes these response parameters cannot be obtained by interpolation. If, for instance, all of the PGs in a given row exceed +50, then none of the three parameters can be obtained by interpolation. In such a case, the value given for each response parameter is the highest concentration tested and is preceded by a ">" sign. This practice is extended similarly to the other possible situations where a response parameter cannot be obtained by interpolation.

The test compound could also be tested in an *in vivo* assay using a hollow fiber test system. This system consists of twelve selected human tumour cell lines encased in hollow fibers which are implanted into athymic nude mice. Six to eight days after administration of the test compound to the mice, the fibers are collected, the cells removed and growth inhibition is measured using MTT. Compounds which produce promising results in this assay may be selected for further *in vivo* evaluation using e.g. xenograft models.

CLAIMS

1. Compounds of the general formula I



I

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each independently are:

hydrogen;

halogen;

nitro;

nitroso;

cyano;

a group $-CO-Z-R^{10}$, $-CS-Z-R^{10}$ or $-SO_2-Z-R^{10}$ wherein Z is $-O-$, $-S-$ or $-N(R^{11})-$;

a group $-C(NH)-NR^{10}R^{11}$;

a group $-CO-R^{10}$, $-SO-R^{10}$ or $-SO_2-R^{10}$;

a group $-Z-CO-R^{10}$, $-Z-CO-Z-R^{10}$, $-Z-CS-R^{10}$ or $-Z-SO_2-R^{10}$ wherein each Z independently is as defined above;

a group $-O-R^{10}$ or $-S-R^{10}$;

a group $-NR^{10}R^{11}$;

where groups R^{10} and R^{11} each independently are hydrogen or is optionally substituted C_{1-8}alkyl, aryl, aryl-C_{1-8}alkyl where an alkyl group or moiety may be interrupted by $-O-$, $-S-$ or $-N(R^{14})-$ wherein R^{14} is hydrogen, C_{1-8}alkyl or aryl, and where the optional substituent(s) are selected from halogen, nitro, amidine, cyano, mercapto, C_{1-8}alkylthio, arylthio, hydroxy, C_{1-8}alkoxy, aryloxy, amino, C_{1-8}alkylamino, arylamino, diC_{1-8}alkylamino, diarylamino, formyl, C_{1-8}alkylcarbonyl, arylcarbonyl, C_{1-8}alkoxycarbonyl, aryloxycarbonyl, C_{1-8}alkylcarbonyloxy, aryloxycarbonyloxy, or two neighbouring substituents together

form a bivalent group -Z-$(C(R^{15})_2)_m$-Z- wherein each Z independently is as defined above, R^{15} is hydrogen or C_{1-2}alkyl, and m is an integer from 1 to 3;

optionally substituted, linear or branched C_{1-10}alkyl, optionally substituted, linear or branched C_{2-10}alkenyl or C_{4-10}alkadienyl or C_{6-10}alkatrienyl, optionally substituted, linear or branched C_{2-10}alkynyl, or optionally substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkadienyl, C_{6-8}cycloalkatrienyl or C_{3-8}cycloalkyl-C_{1-4}alkyl where the optional substituent(s) are selected from halogen, nitro, cyano, -CO-Z-R^{10}, -SO_2-Z-R^{10}, -CO-R^{10}, -SO-R^{10}, -SO_2-R^{10}, -Z-CO-R^{10}, -Z-SO_2-R^{10}, -O-R^{10}, -S-R^{10}, and -$NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;

aryl or aryl-C_{1-4}-alkyl where the aryl moiety may be substituted from 1 to 6 substituents selected from C_{1-4}-alkyl, halogen, nitro, nitroso, cyano, a group -CO-Z-R^{10}, -CO-Z-R^{10}, -SO_2-Z-R^{10}, -CO-R^{10}, -SO-R^{10}, -SO_2-R^{10}, -Z-CO-R^{10}, -Z-SO_2-R^{10}, -O-R^{10}, -S-R^{10}, or -$NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;

or R^3 and R^7, and/or R^4 and R^8 together forms a bond;

or R^1 and R^2, and/or R^5 and R^6 together forms a bivalent group -$(CH_2)_n$- wherein n is an integer from 3 to 5, or a bivalent group -Z-$(C(R^{15})_2)_m$-Z- wherein Z, R^{15} and m is as defined above;

X^1 and X^2 each independently is O, S, or N(R^{12}), wherein R^{12} is a group as defined for R^{10}; and

Y^1 and Y^2 each independently is N or C(R^{13}) wherein R^{13} is a group as defined for R^{10} above;

with the proviso that when X^1-Y^1 and X^2-Y^2 are both O-N, and R^3 and R^7 together forms a bond, and R^4 and R^8 together forms a bond, then

at least one of R^1, R^2, R^5, and R^6 is different from hydrogen, or

R^1 and R^6 are both different from nitro, methyl and unsubstituted phenyl;

and physiologically acceptable salts thereof.

2. Compounds according to claim 1 wherein X^1-Y^1 and X^2-Y^2 are both O-N.

3. Compounds according to claim 1 or 2 wherein R^3 and R^7 together form a bond, and/or R^4 and R^8 together form a bond.

4. Compounds according to any of claims 1-3 wherein R^2 and R^5 are both hydrogen.

5. Compounds according to any of claims 1-4 wherein R^1 and R^6 independently are unsubstituted or substituted aryl groups, preferably phenyl substituted with one to four groups selected from hydroxy, halogen, amino, alkylamino, dialkylamino, mercapto, alkylthio, nitro, sulfonyl, C_{1-8}alkoxy, C_{1-8}alkyl-or arylcarbonyloxy, C_{1-8}alkyl- or arylcarbonylamino, C_{1-8}alkyl- or arylsulfonylamino, or two neighbouring substituents together form a bivalent group -Z-$(C(R^{15})_2)_m$-Z-.

6. A compound according to any of claims 1-5 selected from
5,5'-bis-(3-(4''-hydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-hydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-hydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-dihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-trihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-trihydroxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-dimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-trimethoxyphenyl)-isoxazole),

5,5'-bis-(3-(3'',4'',5''-trimethoxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-acetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-acetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-acetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-diacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-triacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-triacetoxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-benzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2''-benzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-benzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',4''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',5''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',5''-dibenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(2'',3'',4''-tribenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4'',5''-tribenzyloxyphenyl)-isoxazole),
5,5'-bis-(3-(3''-hydroxy-4''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(4''-hydroxy-3''-methoxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-methylendioxyphenyl)-isoxazole),
5,5'-bis-(3-(3'',4''-(2,2-propylendioxy)phenyl)-isoxazole),
5,5'-bis-(3-(4''-nitrophenyl)-isoxazole),
5,5'-bis-(3-(4''-aminophenyl)-isoxazole),
5,5'-bis-(3-(4''-acetaminophenyl)-isoxazole),
5,5'-bis-(3-(4''-chlorophenyl)-isoxazole),
5,5'-bis-(3-(4''-bromophenyl)-isoxazole),
5,5'-bis-(3-(4''-iodophenyl)-isoxazole),
5,5'-bis-(3-(4''-sulfonylphenyl)-isoxazole),
5,5'-bis-(3-(4''-amidinophenyl)-isoxazole), and
5,5'-bis-(3-(4''-carboxyphenyl)-isoxazole).

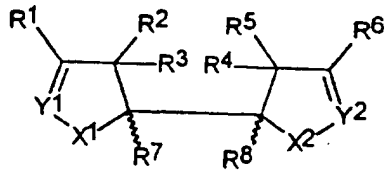
7. A compound of the general formula I as defined in claim 1 which, when tested against a mammalian cancer cell line in accordance with the standard procedure of the National Cancer Institute *in vitro* Anticancer Drug Discovery Screen, results

in a Percentage Growth (PG), as defined herein, below 90, preferably 80, in particular 70, especially 60, such as 50.

8. A compound of the general formula I as defined in claim 1 which, when tested against a mammalian cancer cell line in accordance with the standard procedure of the National Cancer Institute *in vitro* Anticancer Drug Discovery Screen, exhibits a Response Parameter GI50 value, as defined herein, at a concentration of at the most 10^{-4} M with respect to at least one mammalian cancer cell line.

9. A compound of the general formula I as defined in claim 1 which, when tested against a mammalian cancer cell line in accordance with the standard procedure of the National Cancer Institute *in vitro* Anticancer Drug Discovery Screen, does not exhibit a LC50 value, as defined herein, at a concentration of below 10^{-4} M.

10. A pharmaceutical composition comprising at least one of the compounds of the general formula I'



I'

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each independently are:

hydrogen;

halogen;

nitro;

nitroso;

cyano;

a group $-CO-Z-R^{10}$, $-CS-Z-R^{10}$ or $-SO_2-Z-R^{10}$ wherein Z is $-O-$, $-S-$ or $-N(R^{11})-$;

a group $-C(NH)-NR^{10}R^{11}$;

a group $-CO-R^{10}$, $-SO-R^{10}$ or $-SO_2-R^{10}$;
a group $-Z-CO-R^{10}$, $-Z-CO-Z-R^{10}$, $-Z-CS-R^{10}$ or $-Z-SO_2-R^{10}$ wherein each Z independently is as defined above;
a group $-O-R^{10}$ or $-S-R^{10}$;
a group $-NR^{10}R^{11}$;
where groups R^{10} and R^{11} each independently are hydrogen or is optionally substituted C_{1-8}alkyl, aryl, aryl-C_{1-8}alkyl where an alkyl group or moiety may be interrupted by -O-, -S- or $-N(R^{14})-$ wherein R^{14} is hydrogen, C_{1-8}alkyl or aryl, and where the optional substituent(s) are selected from halogen, nitro, amidine, cyano, mercapto, C_{1-8}alkylthio, arylthio, hydroxy, C_{1-8}alkoxy, aryloxy, amino, C_{1-8}alkylamino, arylamino, diC_{1-8}alkylamino, diarylamino, formyl, C_{1-8}alkylcarbonyl, arylcarbonyl, C_{1-8}alkoxycarbonyl, aryloxycarbonyl, C_{1-8}alkylcarbonyloxy, aryloxycarbonyloxy, or two neighbouring substituents together form a bivalent group $-Z-(C(R^{15})_2)_m-Z-$ wherein each Z independently is as defined above, R^{15} is hydrogen or C_{1-2}alkyl, and m is an integer from 1 to 3;
optionally substituted, linear or branched C_{1-10}alkyl, optionally substituted, linear or branched C_{2-10}alkenyl or C_{4-10}alkadienyl or C_{6-10}alkatrienyl, optionally substituted, linear or branched C_{2-10}alkynyl, or optionally substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkadienyl, C_{6-8}cycloalkatrienyl or C_{3-8}cycloalkyl-C_{1-4}alkyl where the optional substituent(s) are selected from halogen, nitro, cyano, $-CO-Z-R^{10}$, $-SO_2-Z-R^{10}$, $-CO-R^{10}$, $-SO-R^{10}$, $-SO_2-R^{10}$, $-Z-CO-R^{10}$, $-Z-SO_2-R^{10}$, $-O-R^{10}$, $-S-R^{10}$, and $-NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;
aryl or aryl-C_{1-4}-alkyl where the aryl moiety may be substituted from 1 to 6 substituents selected from C_{1-4}-alkyl, halogen, nitro, nitroso, cyano, a group $-CO-Z-R^{10}$, $-CO-Z-R^{10}$, $-SO_2-Z-R^{10}$, $-CO-R^{10}$, $-SO-R^{10}$, $-SO_2-R^{10}$, $-Z-CO-R^{10}$, $-Z-SO_2-R^{10}$, $-O-R^{10}$, $-S-R^{10}$, or $-NR^{10}R^{11}$ wherein Z, R^{10} and R^{11} are as defined above;
or R^3 and R^7, and/or R^4 and R^8 together forms a bond;

or R^1 and R^2, and/or R^5 and R^6 together forms a bivalent group $-(CH_2)_n-$ wherein n is an integer from 3 to 5, or a bivalent group $-Z-(C(R^{15})_2)_m-Z-$ wherein Z, R^{15} and m is as defined above;

X^1 and X^2 each independently is O, S, or $N(R^{12})$, wherein R^{12} is a group as defined for R^{10} above; and

Y^1 and Y^2 each independently is N or $C(R^{13})$ wherein R^{13} is a group as defined for R^{10} above;

in combination with a pharmaceutically acceptable carrier.

11. The compounds of the general formula I' as defined in claim 10 for use in therapy, in particular in the treatment of cancer.

12. A method for the treatment of cancer in human beings or animals, said method comprising administering to a human being or animal in need thereof an effective amount of a compound of the general formula I' as defined in claim 10.

13. The use of a compound of the general formula I' as defined in claim 10 in the manufacture of a medicament for use in the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00112

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 261/08, A61K 31/42
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CASONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of heterocyclic chemistry, Volume 12, No 6, December 1975, Ronda M. Sandifer et al, "The Reactions of C(alpha), O-Dilithiooximes, C(alpha), N-Dilithiophenylhydrazones, and C(alpha),N, N-Trilithiohydrazones with Diethyl Oxalate to Give Biisoxazoles,Bipyrazoles, and Pyridazones", page 1159 - page 1163, compounds 18-21,23	1-6
	--	
X	Chemical Abstracts, Volume 65, No 2, 18 July 1966 (18.07.66), (Columbus, Ohio, USA), V.N. Chistokletov et al, "1,3-Dipolar addition to unsaturated compounds. XIII. Addition of N-oxides of nitriles and nitrilimines to 1,2- and 2, 3-di-chloro-1,3-butadienes", page 2243-2244, THE ABSTRACT No 2244g, Zh.Organ.Khim 1966, 2 (2), 201-206	1-6
	--	

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 1997	05 -07- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00112

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 54, 10 July 1960 (10.07.60), (Columbus, Ohio, USA), Paolo Grünanger et al, "Synthesis of 5,5'-biisoxazoles and 5, 5'-biisoxazolealkanes", page 13097-13098, THE ABSTRACT No 13098b, Gazz.chim.ital 1959, 89, 598-614	1-6
	--	
X	Chemical Abstracts, Volume 54, No 4, 25 February 1960 (25.02.60), (Columbus, Ohio, USA), Paolo Grünanger et al, "The reaction of fulminic acid with diacetylene", page 3379--3380, THE ABSTRACT No 3380f, Atti accad.nazl.Lincei Rend. ... 1959, 26, 235-239	1-5
	--	
X	Chemical Abstracts, Volume 54, No 17, 10 Sept 1960 (10.09.60), (Columbus, Ohio, USA), Giorgio Guadiano et al, "Biisoxazoles", page 17367-17368, THE ABSTRACT No 17368i, Atti accad. nazl Lincei.Rend. ... 1959, 26, 164-171	1-5
	--	
X	Chemical Abstracts, Volume 56, No 11, 28 May 1962 (28.05.62), (Columbus, Ohio, USA), Pierfrancesco Bravo et al, "A new synthesis of 3-chloroisoxazoles", page 12869-12870, THE ABSTRACT No 12869e, Gazz.Chim.Ital. 1961, 91, 47-64	1-5
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00112

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claims Nos.: 1,10 and 7-9
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 1 and 10 are to broadly formulated to permit a meaningful search. The search has therefore been limited to bis-isoxazoles, as all the exemples are bis-isoxazoles. The formulation of claims 7-9 are not clear (see PCT Rule 6). The claims has been searched as if they were directed to a compound with anticancer or pharmaceutical effect (1:st medical indication).

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.